REMARKS

Reconsideration and withdrawal of the rejections of the application are requested in view of the amendments and remarks presented herein, which place the application into condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 63-81 are pending in this application. Support for the added claims can be found throughout the specification and from the cancelled claims. Particular support for "replication defective retroviral vector" can be found, for example, on page 14, line 2. No new matter is added.

It is submitted that the claims are patentably distinct over the prior art and that these claim are and were in full compliance with the requirements of 35 U.S.C. §112. The amendments of the claims herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather, the amendments are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the amendments should not give rise to any estoppel, as they are not narrowing amendments.

Priority

The specification has been amended to reflect the issuance of U.S. Patent No. 6,669,936 in the lineage of the present application. Applicants request that the Examiner acknowledge the claims for foreign priority.

Information Disclosure Statement

The Examiner is correct regarding reference AG on the IDS of March 11, 2003. WO 91/197998 is a typographical error for WO 91/19798. The Examiner is thanked for his thorough review of the PTO-1449 forms.

Claim Objections

The objection to claim 49 is moot in view of its cancellation.

II. THE REJECTION UNDER 35 U.S.C. § 112, 2ND PARAGRAPH, IS OVERCOME

Claims 46-51 and 61 were rejected under the second paragraph of Section 112 as allegedly being indefinite. The Examiner questioned the recitation of "functionally active rev" in the method claims. Claims 46-51 and 61 have been cancelled, and the newly added method

claims do not recite "functionally active rev." Therefore, the rejection has been obviated and its reconsideration and withdrawal are requested.

III. THE CLAIMED INVENTION AND THE STATE OF THE ART

The claimed invention is drawn to a lentivirus-based retroviral production system for the production of a replication defective retroviral vector. The replication defective retroviral vectors of the claimed invention find use as gene delivery tools and therefore are distinct from wild-type lentivirus, where viral proteins are simply mutated and studied through mutational analyses. These wild-type viruses are not generated through the use of a lentivirus-based retroviral vector production system that is capable of producing a replication defective retroviral vector, and which therefore finds use as a safe and effective gene delivery vehicle.

The inventors' own work, published in January 1998 (Kim *et al.*, J. Virol., 72:811-816; of record), detailed the first lentivirus-based retroviral production system that eliminated functional Tat from the vector production system. This work is also the subject matter of the instant disclosure. Tat was known to be essential for viral replication and had been expressed in all of the previously reported production systems. See col. 1, page 812 of Kim *et al.*

The state of the art in 1997 was a second generation-type lentiviral vector system, which was reduced to HIV-derived components *gag/pol*, *tat* and *rev* genes. It was believed, at that time, that only in the presence of Tat and Rev would the HIV structural genes be expressed and new viral particles produced. See col. 2, page 8463 of Dull *et al.* (J. Virol., 72:8463-8471; 1998; copy enclosed). Therefore, a lentivirus-based retroviral vector production system without functional Tat was not in existence until it was the subject matter of the instant specification, and further was not in the public domain until the inventors' published their work in January 1998.

IV. THE REJECTIONS UNDER 35 U.S.C. § 102 ARE OVERCOME

Claims 20-40, 42-44, 46-50, 52 and 60-62 were rejected under Section 102(b) as allegedly being anticipated by Harmache *et al.* as evidenced by Douvas *et al.* The rejection is traversed.

Harmache fails to teach or suggest the claimed lentivirus-based retroviral vector production system lacking functional Tat. Harmache teaches a mutational analysis of wild-type CAEV virus and mutates Tat to determine its effect on viral replication in goat cells. Harmache teaches that Tat is necessary for viral replication in certain goat cells and that Tat-dispensibility is highly dependent on cell type (*i.e.*, goat cell type), origin, and differentiation and activation

state. See page 5452, 2nd column. Therefore, Harmache fails to teach or suggest the use of a lentivirus-based retroviral vector production system lacking functional Tat for the production of a replication defective retroviral vector. In fact, Harmache concludes that the CAEV virus can replicate without the *tat* gene and that transactivation is not the main function of Tat in CAEV infection. See page 5452, col. 1. Therefore, the CAEV Tat mutants of Harmache were not produced from a lentivirus-based retroviral production system capable of producing a replication defective vector.

Claims 20-22, 24, 25, 27-30, 33-36, 40, 42-44, 46-50, 52-54 and 56-60 were rejected under Section 102(b) as allegedly being anticipated by Bray *et al.* The rejection is traversed.

Bray teaches HIV proviral constructs that produce replication-competent virus in the absence of Rev, due to the functional replacement of the Rev/RRE interaction with a constitutive transport element (CTE). The lentiviral system of Bray includes the viral accessory gene *tat* as well as other viral accessory genes *vif*, *vpr*, *vpu*, and *nef*. See Figure 5A, page 1259. Therefore, the HIV lentivirus of Bray is not a lentivirus-based retroviral vector production system, which lacks functional tat and which is capable of producing a replication defective retroviral vector. Furthermore, there is no teaching or suggestion in Bray of how to make the *tat* gene non-functional in the vector system, as the Bray teachings focus on rev-independence and the functional replacement of the Rev/RRE interaction with MPMV CTE.

Claims 20-51 and 53-55 were rejected under Section 102(e) as allegedly being anticipated by Verma *et al.* as evidenced by any one of Coffin *et al.*, Carrano *et al.*, Zagury *et al.* or Cohen *et al.* The rejection is traversed.

As the Examiner pointed out on page 9 of the Office Action, "Verma did not explicitly suggest deletion or disruption of tat genes." Independent claim 63 of the present application contains the limitation, "wherein the retroviral vector production system lacks nucleic acid sequences encoding functional tat." Therefore, Verma, by the Examiner's own admission, does not anticipate the invention as claimed.

Claims 20-22, 25-30, 32-36, 38-54 and 60-62 were rejected under Section 102(b) as allegedly being anticipated by Chang *et al.* The rejection is traversed.

Chang teaches HIV lentivirus Tat(-) mutants which retain their ability to replicate, at least at some altered level. Therefore, the HIV Tat mutants of Chang were not produced from a

lentivirus-based retroviral production system which is capable of producing a replication defective vector.

Reconsideration and withdrawal of the Section 102 rejections are requested.

V. THE REJECTIONS UNDER 35 U.S.C. § 103 ARE OVERCOME

Claims 20-51 and 53-55 were rejected under Section 103(a) as allegedly being unpatentable over Verma in view of Chang *et al.* The rejection is traversed.

As discussed above, Verma does not teach or suggest deletion or disruption of tat genes, and Chang does not teach or suggest a replication-defective vector. The skilled artisan could not combine Verma and Chang to arrive at the present invention because the Tat mutants of Chang were shown to be replication-competent.

Claims 56-59 were rejected under Section 103(a) as allegedly being unpatentable over Hammarskjold *et al.* in view of Chang *et al.* and in further view of Bray *et al.* The rejection is traversed.

Hammarskjold teaches the replication competent HIV lentivirus Rev(-) mutants of Bray. The teachings of Bray and Hammarskjold relate to the study and quest for a replication competent HIV virus which is safer (acting through Rev-independence) for the purpose of using the virus as a vaccine. Likewise, the teachings of Chang teach replication competent HIV Tat(-) virus for the purpose of establishing a safe, attenuated, whole-HIV vaccine. There are no teachings or suggestions in any of the cited references, alone or in combination, to extend what is taught such that one would be able to make and use, with a reasonable expectation of success, a lentivirus-based retroviral production system, which lacks functional Tat and which is capable of producing a replication defective vector. At the very most, the combination of the teachings relies on hindsight determination.

As the Examiner is aware, it is well established that the cited references must provide the incentive or motivation for modifying the reference teachings to arrive at the invention. *See e.g.*, *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) ("The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification."); *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). No such motivation is provided in the cited references. In fact, the state of the art supports this observation because lentivirus-based retroviral vector production systems lacking functional Tat, which were capable of producing replication defective retroviral vectors,

were not in existence until it was the subject matter of the instant specification. In addition, such systems were not in the public domain until the inventors published their work in January 1998, as discussed above.

Therefore, a *prima facie* case of obviousness has not been made. Accordingly, reconsideration and withdrawal of the Section 103 rejections are requested.

VI. THE DOUBLE PATENTING REJECTIONSARE OVERCOME

Claims 20-62 were rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-71 of U.S. Patent No. 6,312,682 and over claims 1-71 of U.S. Patent No. 6,669,936. A Terminal Disclaimer to both patents is enclosed, obviating the double patenting rejections. Reconsideration and withdrawal are requested.

REQUEST FOR INTERVIEW

Applicants would be pleased to discuss their rationale in preparing this Response, at the Examiner's convenience, prior to the issuance of any further papers, in an effort to expedite allowance of the claims. It is requested that the Examiner contact the undersigned when he is ready to work on this application so that an interview can be arranged.

CONCLUSION

Applicants believe that the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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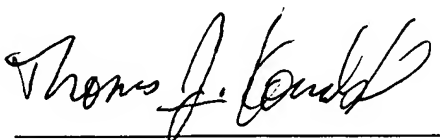
By: 

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